IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AFFYMETRIX, INC., Plaintiff/Counter-Defendant, v. ILLUMINA, INC., Defendant/Counter-Plaintiff.	C.A. No. 04-901-JJF **REDACTED VERSION**

PLAINTIFF AFFYMETRIX, INC.'S STATEMENT OF DISPUTED MATERIAL FACTS IN RESPONSE TO ILLUMINA, INC.'S MOTION FOR SUMMARY JUDGMENT OF INVALIDITY OF THE ASSERTED CLAIMS OF THE '531 PATENT

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INTRODUCTION

1. Pursuant to this Court's Memorandum Order on Summary Judgment Procedure, Plaintiff Affymetrix, Inc. ("Affymetrix") submits this Counter-Statement certifying that genuine issues of material fact exist and setting forth such disputed facts in opposition to Defendant Illumina, Inc.'s ("Illumina") Motion For Summary Judgment of Invalidity of the Asserted Claims of the '531 Patent. (D.I. 275, 276).

2. Illumina argues that U.S. Patent No. 5,545,531 (the "'531 patent") is invalid under 35 U.S.C. § 102 as anticipated by PCT Patent Application WO 93/17126 (the "'126 PCT application"). In seeking to invalidate claims of a patent, Illumina bears the burden of establishing the invalidity of those claims by clear and convincing evidence. *See, e.g., Avia Group Int'l, Inc. v. L.A. Gear Cal., Inc.*, 853 F.2d 1557, 1562 (Fed. Cir. 1988) ("[A] challenger must establish facts, by clear and convincing evidence, which persuasively lead to the conclusion of invalidity.").

3. Disputed issues of fact exist with respect to at least three aspects of what the '126 PCT application would have disclosed to the person of ordinary skill in the art and whether such a disclosure anticipates the elements of the '531 claims. First, the '126 PCT application is directed to creating "sectioned arrays" which are *not* the array of arrays Illumina suggests them to be, but rather a collection of wells in which biological assays are used to fractionate a sample. Second, the few lines (out of 100 pages) from the '126 PCT application upon which Illumina relies do not disclose attaching a wafer with a plurality of probe arrays to a body (claims 1 and 2) or applying a material resistant to the flow of a liquid sample so as to surround the probe arrays, thereby creating test wells (claims 3 and 4). Third, these sentences do not, as Illumina suggests, disclose exposing

the wafer to spaces of the wells (claims 1 and 2) or creating test wells (claims 3 and 4). Thus, the '126 PCT application does not disclose the invention of the '531 patent and could not be used to create a biological chip plate as described by the '531 patent.

4. Of course, none of this is surprising given that neither of the named inventors of the '126 PCT application ever made a microarray.

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5. Furthermore, Illumina only offers attorney argument about the reference and no testimony regarding what a person skilled in the art would believe was disclosed by the '126 PCT application or even what level of skill such a person would have. This failure of proof, in and of itself, should lead to a denial of their motion.

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[1] Affymetrix's exhibits attached to this Counter-Statement are lettered, while Illumina's exhibits were numbered.

I. SEVERAL DISPUTED ISSUES OF FACT EXIST REGARDING WHETHER THE '126 PCT APPLICATION DISCLOSES ALL ELEMENTS OF THE '531 PATENT

6. Whether a claim is anticipated by a particular prior art reference is a question of fact. *Diversitech Corp. v. Century Steps, Inc.*, 850 F.2d 675, 677 (Fed. Cir. 1988). What a prior art reference teaches or discloses is also a question of fact. *Novo Nordisk Pharm., Inc. v. Bio-Tech. Gen. Corp.*, 424 F.3d 1347, 1355 (Fed. Cir. 2005). Illumina, as the party challenging the validity of the patent, bears the burden of proving anticipation by clear and convincing evidence. *Avia*, 853 F.2d at 1562. There are several factual disputes regarding whether the '126 PCT application anticipates the '531 patent.

A. THE "SECTIONED ARRAYS" OF THE '126 PCT APPLICATION DO NOT INCLUDE A PROBE ARRAY WITHIN EACH WELL

7. Illumina repeatedly points to two sentences of the '126 PCT application for the proposition that sectioned arrays include a wafer with a plurality of probe arrays, each probe array comprising a collection of probes, at least two of which are different, arranged in a spacially defined and physically addressable manner. (*See* Illumina Br., Exh. 1.) These sentences read as follows:

> As used herein an 'oligonucleotide array' is an array of regularly situated areas on a solid support wherein different oligos are immobilized, typically by covalent linkage. Each area contains a different oligo whose location is predetermined.

(Illumina Br., Exh. 3 at 3 (IAFP13430).)

8. Despite Illumina's contention to the contrary, the "sectioned array" disclosed in the '126 PCT application does not include a probe array in each "area" or "well" of the array. Rather, each area or well contains many copies of a single

oligonucleotide of the same sequence. (*See* Declaration of Robin A. Felder (hereinafter "Felder Decl.") at ¶ 10.) The two sentences on which Illumina relies demonstrate that there is not a collection of probes in each area as "[e]ach area contains *a different oligo*." The remainder of the patent disclosure makes this point repeatedly. For example: "The reactions occurring in different wells are highly specific due to the nucleotide sequence of *the immobilized oligo*." (Illumina Br., Exh. 3 at 3 (IAFP13428) (emphasis added).)

9. Figure 1a shows that each well contains a single species of oligonucleotide (with many copies of the same oligo).

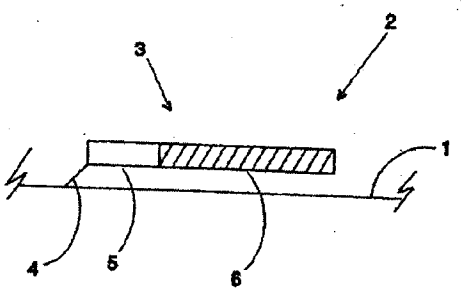

Figure 1a

(Illumina Br., Exh. 3 at 1/14 (IAFP13512).) As the Brief Description of the Drawings states: "Figure 1a shows *an oligo* immobilized in an area of a binary array." (Illumina Br., Exh. 3 at 5 (IAFP13430) (emphasis added).) As the Detailed Description of the Invention states: "Figure 1 shows a substrate or support 1 having immobilized thereon an array of oligos 3, *each oligo being in a separate area 2 of support 1*. Figure 1a shows one area 2. *A binary oligo 3 (many copies, of course)* comprised of constant region 5 and variable region 6 is covalently bound to support 1 by covalent linking moiety 4."

(Illumina Br., Exh. 3 at 6 (IAFP13431) (emphasis added).) Thus the "area" or "well" contains only a single species of oligonucleotide and is not a probe array.[2]

10. Figure 2a likewise shows that each well contains many copies of a single oligonucleotide. (The single oligonucleotide pictured represents a collection of oligonucleotides all of the same sequence.)

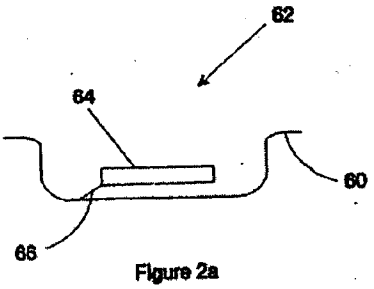

Figure 2a

(Illumina Br., Exh. 3 at 2/14 (IAFP13513).) As the Brief Description of the Drawings states: "Figure 2a shows a well of a sectioned array." (Illumina Br., Exh. 3 at 5 (IAFP13430) (emphasis added).) As the Detailed Description of the Invention states: "Figure 2 shows a support sheet 60 having an array of depressions or wells 62, *each containing many copies of an immobilized oligo 64*. Figure 2a shows one well 62 of the array of Figure 2." (Illumina Br., Exh. 3 at 7 (IAFP13432) (emphasis added).) Thus,

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2 The unusual nomenclature "binary array" does not imply two different oligonucleotides in each area or well. Rather, as shown in Figure 1a, a "binary array" is simply an array of oligonucleotides where the individual oligonucleotides have two different segments of sequence – one that is the same in every well, and a second portion that differs from well to well. (Illumina Br., Exh. 3 at 6 (IAFP13431).)

again, the "area" or "well" contains only a single species of oligonucleotide and is not a probe array.[3]

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Dr. Rava repeated the point later:

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[3] Although discussed nowhere in the specification, Illumina identified a single dependent claim that states "A sectioned array according to claim 24 wherein not all oligonucleotides in each area are of the same sequence." (Illumina Br., Exh. 3 at 60 (IAFP13485).) There is no disclosure in the application discussing attaching oligonucleotides of more than one sequence to one location in the sectioned array. Furthermore, given that the sectioned array was designed to provide wells for different reactions (rather than to detect hybridization events), there would be no reason to create a probe array in each well pursuant to this application. (Illumina Br., Exh. 3 at 59 (IAFP13484) (Claim 24: "…wherein said areas are physically separated from one another into sections, *such that nucleic acids in an aqueous solution generated in one section cannot migrate to another section*…").) Indeed,

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(Exh. B, Rava Depo. at 267:14-17.)

12. Despite the clarity of the patent disclosure and Dr. Rava's testimony,

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13. This exchange illustrates that the '126 PCT application in fact does not disclose any invention claimed in the '531 patent. The point of creating wells in the "sectioned array" disclosed in the '126 PCT application was to isolate distinct, individual oligonucleotide sequences into each segregated region. Each area or well in the sectioned array is used to isolate an analyte. The single oligonucleotide probe sequence in each well is then used to purify a complimentary target sequence within each analyte out of a mixture as complex as an entire genome. In effect, the single species of oligonucleotide attached at the bottom of each well of the '126 PCT application serves as a "primer" for additional biochemical reactions for the purpose of creating a purified sample population within the well. This is the opposite of the '531 application, which teaches a method for creating a device specifically directed to isolate a sample matched to a specific probe array *for the purpose of detecting hybridization events* between the sample and the probe array, where there are a plurality of probe arrays.

14. Affymetrix's expert, Dr. Robin Felder, will opine and testify at trial that the '126 PCT application's discussion of sectioned arrays and binary arrays does not disclose a plurality of probe arrays in a well. (Felder Decl. at ¶ 10).

15. Accordingly, there is a factual dispute regarding whether the '126 PCT application's discussion of a "sectioned array" discloses a "wafer comprising on its surface a plurality of probe arrays, each probe array comprising a collection of probes, at least two of which are different, arranged in a spacially defined and physically addressable manner," which is a limitation of each of the asserted claims of the '531 patent.

B. THE '126 PCT APPLICATION DOES NOT DISCLOSE ATTACHING A WAFER WITH A PLURALITY OF PROBE ARRAYS TO A BODY OR APPLYING A MATERIAL RESISTANT TO THE FLOW OF A LIQUID SAMPLE SO AS TO SURROUND THE PROBE ARRAYS

16. Claims 1 and 2 of the '531 patent require "attaching the wafer to the body." Claims 3 and 4 require "applying a material resistant to the flow of a liquid sample so as to surround the probe arrays." Illumina relies on a few additional sentences and the related Figures 3 and 7 to argue that these limitations are found in the '126 PCT application. (*See* Illumina Br., Exh. 1.) These sentences read as follows:

> Referring to Figure 7, partialing array 31, comprising an array of wells 31a, is surveyed using sheet 43, having printed thereon an array of miniaturized survey arrays 42. The pattern of arrays 42 corresponds to the pattern of wells 31a, whereby all wells 31a can be surveyed simultaneously.

(Illumina Br., Exh. 3 at 20 (IAFP13445).)

17. In all of its 100 pages, the '126 PCT application contains no disclosure of how to construct what they describe as a "survey array," how to attach a survey array to a body to create a biological chip plate, or how to apply a material to the survey array. Indeed, the only reference regarding the construction of the '126 PCT application's desired "survey array" is to the 1991 *Science* publication of Dr. Fodor (Affymetrix's founder and CEO) *et al.*, on page 20 of the application and reads in its entirety:

> Automated photolithography techniques for preparing miniature oligo arrays have been developed [Fodor, S.P., Read, J.L., Pirrung, M.C., Stryer, L., Lu, A.T., and Solas, D (1991). Light-Directed, Spatially Addressable Parallel Chemical Synthesis, *Science* 251, 767-773]. The manufacture of miniature arrays on a "chip", for use in surveys has also been reported.

(Illumina Br., Exh. 3 at 20 (IAFP13445).)[4]

18. As Dr. Rava testified,

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[4] For a reference to be anticipatory, it must be enabled. *Helifix Ltd. v. Blok-Lok, Ltd.*, 208 F.3d 1339, 1347-48 (Fed. Cir. 2000). As noted above, the only disclosure regarding making survey arrays in the '126 PCT application is a reference to the Fodor *et. al. Science* article. Elsewhere (*e.g.*, in its interrogatory responses in this case), Illumina has argued that Affymetrix's patents, which describe VLSIPS in much more detail than the *Science* article, are not enabled. By arguing that the '126 PCT application is invalidating (and therefore enabled) prior art, Illumina apparently concedes that Fodor et al.s 4 page *Science* article, in and of itself, would enable one of ordinary skill in the art to make and use oligo arrays.

19. Figure 7 of the '126 PCT application depicts a flexible "survey array" placed on top of a "partialing array." There is no indication whatsoever how one would "attach" (claims 1 and 2) or "apply . . . so as to surround the probe arrays" (claims 3 and 4) the "survey array" to the partialing array such that hybridization could occur. (*See* Felder Decl. at ¶ 11.) Indeed, hybridization could not occur unless the device was turned upside down, indicating the importance of attachment or application to surround the probe arrays. The figure itself shows the "survey array" peeling back from the "partialing array" – confirmation that there is no attachment or application.

20. Similarly, the other snippet from the '126 PCT application upon which Illumina relies does not describe application of a material resistant to the flow of a liquid sample so as to surround the probe arrays, as required by claims 3 and 4. Illumina points to Figure 3 and associated text, but that figure shows a lattice structure which sits atop a "sectioned array" and separates one well from another. (Illumina's Br., Exh. 3 at 7 (IAFP13432).) As discussed above, a "sectioned array" does not have a plurality of probe arrays because it contains only one sequence per well. Therefore, the figure and accompanying text do not disclose "applying a material resistant to the flow of a liquid sample *so as to surround the probe arrays*."

21. Affymetrix's expert, Dr. Robin Felder, will opine and testify at trial that the '126 PCT application does not disclose attaching a wafer with a plurality of probe arrays to a body or applying a material resistant to the flow of a liquid sample so as to surround the probe arrays. (Felder Decl. at ¶ 11).

22. For each of these reasons, there are factual disputes regarding whether the '126 PCT Application discloses the "attaching" and "applying" limitations required by the claims of the '531 patent.

C. THE '126 PCT APPLICATION DOES NOT DISCLOSE EXPOSING THE PROBE ARRAYS ON THE WAFER TO THE SPACES OF THE WELLS OR CREATING TEST WELLS

23. Illumina relies on the same snippets to argue that the '126 PCT application discloses "that the probe arrays are exposed to the spaces of the wells" (claims 1 and 2) and "thereby creating test wells" (claims 3 and 4). These limitations allow hybridization to occur between each probe array and a sample solution. Illumina points to the following sentence:

> The pattern of arrays 42 corresponds to the pattern of wells 31a, whereby all wells 31a can be surveyed simultaneously.

(Illumina Br., Exh. 3 at 20 (IAFP13445).). But neither this sentence, nor any other disclosure in the '126 PCT application, explains how this supposed simultaneous survey could occur.

24. If oligonucleotides are, in one instance, attached covalently to the bottom of the wells, and, in the other instance, are attached to the survey array, then they cannot mix together or hybridize. In fact, if drawn properly to scale, there would be orders of magnitude of distance between the oligonucleotides attached to the respective surfaces.

25. Even if one imagined a fluid sample within the sectioned array that was not attached to the area or wells, the '126 PCT application still fails to disclose how the sample would contact the survey array in a fashion suitable for mixing and

hybridization.[5] (Felder Decl. at ¶ 12.) In fact, the only disclosure in the '126 PCT application differs from the '531 by suggesting that the fluids in the wells could be extracted out of the wells and applied to another array by, for instance, "printing" (*i.e.*, dipping a "pen" into the well and then contacting that pin to another array). (Illumina Br., Exh. 3 at 3 (IAFP13428) ("Nucleic acids prepared on a sectioned array can be transferred to other arrays (replicated) by direct blotting of the wells' contents (printing), without mixing the contents of different wells of the array.").) Even if one placed the "survey array" across the top of the "sectioned array" as depicted in Figure 7, there is no disclosure as to how the fluids in the wells of the sectioned array would be able to interact with the "survey array" – especially without mixing of fluids between the wells. This is especially so given the requirements for an effective hybridization reaction on a microarray (which typically requires many hours of constant contact of the fluid with the array with some form of agitation to encourage mixing and some form of temperature control).

26. Illumina also points to Figure 3 and related text when arguing that the '126 PCT application discloses "creating test wells" around each probe array (claims 3

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[5] In his deposition, ~~But there is no~~ disclosure in the patent about how the "sheet" would be applied or attached, that it "hermetically seal[ed]" off each section, or how the sample (whether attached or in fluid in the bottom of the well created by the sectioned array) would interact with the "sheet" sitting on top of it. Nor does the application disclose how the "sheet" would be removed from the sectioned array or how it could be read. The issue for anticipation is whether a single reference discloses all of the elements of a claim. Extrinsic evidence, such as the testimony from Dr. Kramer Illumina cites, cannot be used to supplement the disclosure. *See Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991).

and 4). But, once again, the application only discusses this in the context of the *sectioned array*, which is not a probe array. As discussed above, this would result only in test wells surrounding one oligonucleotide sequence, not a probe array with different sequences.

27. Affymetrix's expert, Dr. Robin Felder, will opine and testify at trial that the '126 PCT application does not teach exposing the probe arrays to spaces of the wells or creating test wells around the probe arrays. For each of these reasons, there is yet another disputed issue of fact regarding the disclosure of the '126 PCT application. (Felder Decl. at ¶ 12).

II. ILLUMINA'S MOTION SHOULD BE DENIED BECAUSE IT ADDUCES NO EVIDENCE, MUCH LESS CLEAR AND CONVINCING EVIDENCE, OF ANTICIPATION.

28. As discussed above, whether a claim is anticipated by a particular prior art reference and what a prior art reference teaches or discloses are questions of fact. *Diversitech*, 850 F.2d at 677; *Novo Nordisk*, 424 F.3d at 1355. Illumina, as the party challenging the validity of the patent, bears the burden of proving anticipation by clear and convincing evidence. *Avia*, 853 F.2d at 1562. As courts have discussed in the context of summary judgment on other affirmative defenses, movant must come forward with conclusive evidence. *See, e.g., Torres Vargas v. Santiago Cummings*, 149 F.3d 29, 35-36 (1st Cir. 1998) ("The party who has the burden of proof on a dispositive issue cannot attain summary judgment unless the evidence that he provides on that issue is conclusive.").

29. Illumina has offered *no evidence* regarding the factual issue of what a person skilled in the art would find that the '126 PCT application teaches. Nor has Illumina even attempted to define what level of skill that person would have. Expert

reports have not been exchanged by the parties. Expert depositions have not been conducted. Illumina's motion relies only on attorney argument regarding the disclosure of the application.

30. In the absence of any evidentiary support for Illumina's assertions as to how the person of ordinary skill in the art would have understood the disclosure of the '126 PCT application, Illumina fails to establish by clear and convincing evidence that the '531 patent is anticipated, much less demonstrates that it is entitled to summary judgment on the question.

CONCLUSION

There are several genuine issues of material fact regarding whether the '126 PCT application discloses each of the elements of the asserted claims of the '531 patent. In fact, the analysis above confirms that it does not. In addition, Illumina has failed to adduce any evidence of how a person skilled in the art would understand the '126 PCT application or what level of skill that person would have. For each of these reasons, the Court should deny Illumina's motion for summary judgment without further briefing.

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